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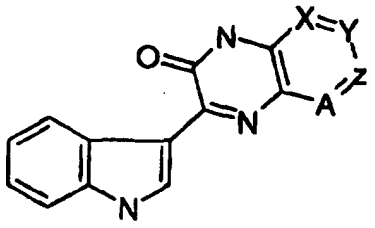
(54) Title: NEW PHARMACEUTICALLY ACTIVE COMPOUNDS

(57) Abstract

The present invention provides optionally substituted and/or annulated compounds of formula (I) wherein X, Y, Z and A is each independently carbon or nitrogen, and at least two of X, Y, Z and A are carbon; and pharmaceutically acceptable salts thereof with the proviso that: 3-(1H-Indol-3-yl)-1H-quinoxalin-2-one, 3-(2-Methyl-1H-indol-3-yl)-1H-quinoxalin-2-one, and 3-(1,2-Diphenyl-1H-indol-3-yl)-1H-quinoxalin-2-one are excluded from compounds of formula (I). The invention includes the use of compounds of formula (I) in medical therapy, particularly in the therapy of conditions requiring inhibition of protein kinase C.



(I)

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NEW PHARMACEUTICALLY ACTIVE COMPOUNDS

The present invention relates to novel compounds which are protein kinase C inhibitors, methods for their preparation, intermediates therefor and pharmaceutical compositions comprising them.

Protein kinase C (PKC) is a family of phospholipid-dependent serine/threonine-specific protein kinases which play an important role in cellular growth control, regulation and differentiation.

Since the activation of PKC has been implicated in several human disease processes, including various forms of cancer, different forms of inflammatory and/or immunological disorders as well as some neurological disorders, inhibition of PKC could be of therapeutic value in treating these conditions.

Several classes of compounds have been identified as PKC inhibitors, e.g. isoquinoline sulphonamides, sphingosine and related sphingolipids, indolocarbazoles and bisindolylmaleimides.

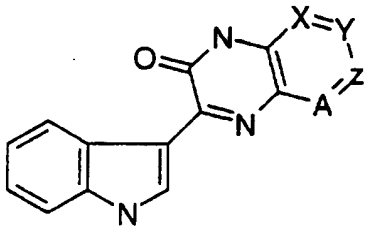
Although PKC inhibitors are described in the prior art, there is a need for specific anti-inflammatory and immunosuppressive compounds which are suitable for oral administration, and for inhalation.

The present invention provides PKC inhibitors, methods for their preparation and intermediates used for their preparation.

The present invention also provides the use of the compounds of the present invention for the treatment of inflammatory, immunological, bronchopulmonary, cardiovascular, oncological or CNS-degenerative disorders.

Also provided by the present invention are pharmaceutical compositions comprising a compound according to the present invention, as active ingredient, together with a pharmaceutically acceptable adjuvant, diluent or carrier.

The present invention provides optionally substituted and/or annulated compounds of formula (I)

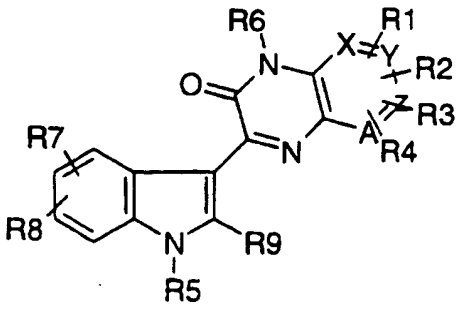


(I)

wherein **X, Y, Z** and **A** is each independently carbon or nitrogen, and at least two of **X, Y, Z** and **A** are carbon;
and pharmaceutically acceptable salts thereof with the proviso that the following compounds are not included in formula (I):

3-(1H-Indol-3-yl)-1H-quinoxalin-2-one,
3-(2-Methyl-1H-indol-3-yl)-1H-quinoxalin-2-one, and
3-(1,2-Diphenyl-1H-indol-3-yl)-1H-quinoxalin-2-one.

Preferred compounds of formula (I) are those of formula (IA):



(IA)

wherein **X**, **Y**, **Z** and **A** are as defined above,

R_1, R_2, R_3, and R_4 is each independently H, hydroxy, amino, nitro, halo, C_{1-6} alkyl, phenylC_{1-6} alkyl, C_{1-6} alkoxy, haloC_{1-6} alkyl, carboxyC_{1-6} alkyl ester or R_1 and R_2 or R_2 and R_3 or R_3 and R_4 form an annulated aromatic ring, or when the atom to which it would be attached is nitrogen, is absent;

R_5 and R_6 is each independently H, C_{1-6} alkyl, hydroxyC_{1-6} alkyl, aminoC_{1-6} alkyl, phenylC_{1-6} alkyl, carboxyC_{1-6} alkyl, C_{1-6} alkenyl, (phenylC_{1-3} alkoxy)C_{1-3} alkyl, (C_{1-6} acyloxy)C_{1-6} alkyl, (C_{1-6} alkoxycarbonyl)C_{1-6} alkyl, (mono- or di-C_{1-6} alkyl)aminoC_{1-6} alkyl , (C_{1-6} alkyl)aminocarbonylC_{1-6} alkyl, (C_{1-6} acylamino)C_{1-6} alkyl, (aminoC_{1-3} alkylphenyl)C_{1-3} alkyl, or aminodeoxysugar;

R_7 and R_8 is each independently H, amino, nitro, hydroxy, halogen, C_{1-6} alkoxy, phenylC_{1-6} alkoxy or carboxyC_{1-6} alkyl ester;

R_9 is H, C_{1-6} alkyl, phenyl, halophenyl or phenylC_{1-6} alkyl and wherein when R_5 and R_9 together comprise 3-5 carbons they may be linked to generate a cyclic moiety which may be aminoC_{1-6} alkyl substituted ;

and wherein at least one of R_1 to R_9 is not H and wherein when the only one of R_1 to R_9 which is not H is R_9, R_9 is not methyl;

and pharmaceutically acceptable salts thereof.

The compounds of formula (IA), in which at least one of R_5 and R_6 carries an amino, carboxy or hydroxy group; and pharmaceutically acceptable salts thereof, may be prepared by,

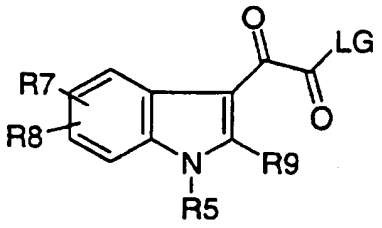
a) deprotecting a compound of formula (II) corresponding to formula (IA) but in which at least one of R_5 and R_6 carries a protected amino, carboxy or hydroxy group, or

b) converting a compound of formula (IA), in which at least one of R_5 and R_6 carries an amino or carboxy group

i) to a pharmaceutically acceptable salt thereof, or vice versa; or

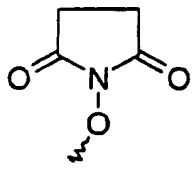
ii) a pharmaceutically acceptable salt of a compound of formula (IA) into a different pharmaceutically acceptable salt.

The compounds of formula (IA), in which R_6 is hydrogen, may be prepared by reacting a compound of formula (III):

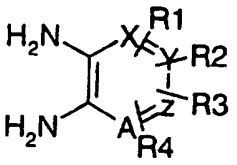


(III)

wherein R_5, R_7, R_8, and R_9 are as defined in formula (IA) and LG is a leaving group, e.g :



with a compound of formula (IV):



(IV)

wherein **A, X, Y,** and **Z** are as defined in formula (I), and R_1-R_4 are as defined in formula (IA), in a suitable solvent, e.g. THF, at about 10-30 °C, e.g. for about 16 hours.

When R_5 in formula (III) carries an amino, carboxy or hydroxy group, these groups should be suitably protected. The protecting groups may be removed in a subsequent deprotecting step.

The compounds of formula (IA), when R_6 is other than H, may be prepared by reacting a compound of formula (II) which corresponds to formula (IA), but in which R_6 is H, with a suitable alkylating agent, e.g methyl iodide in the presence of a base, e.g. sodium hydride. The alkylating step may be carried out in a suitable solvent e.g dimethyl formamide at about 10-30 °C for e.g 2 hours.

When R_5 in formula (II) and/or the alkylating agent carries an amino, carboxy or hydroxy group, such groups should be suitably protected. The protecting groups may be removed in a subsequent deprotecting step.

The compounds of formula (II) may be prepared by

(i) reacting a compound of formula (III), as defined above, with a compound of formula (IV), as defined above, in a suitable solvent e.g.THF, at about 10-30 °C, e.g. for 16 h ,or

(ii) by alkylating the product of (i) with a suitable alkylating agent

when R_5 in formula (III) and/or the alkylating agent carries an amino, carboxy or hydroxy group, these should be in a protected form.

In all processes above, the protecting groups and conditions for deprotection are well known to those skilled in the art. Suitable protecting groups for amino groups are e.g phthaloyl groups and the deprotecting agent may be methylamine in e.g. water. The deprotecting step may be carried out in a suitable solvent, e.g tetrahydrofuran at about 10-30 °C, e.g for about 5 hours. Suitable protecting groups for carboxy groups are e.g t-butyl groups and the deprotection step may be carried out in trifluoro acetic acid at about 10-30 °C, e.g for about 4 hours. The hydroxy groups are protected as their corresponding acetoxy groups and the deprotecting agent may be methylamine in e.g. water. The deprotecting step may be carried out in a suitable solvent, e.g tetrahydrofuran at about 10-30 °C, e.g for about 16 hours.

In process b) the conversion may be carried out by conventional processes, e.g.

i) reaction of the free base with an acid containing the desired anion, or by careful basification of the salt, or

ii) reaction of the free acid with a base containing the desired cation, or by careful acidification of the salt.

The reaction may be carried out in a suitable solvent, e.g. methanol or methylene chloride.

Compounds of formula (I) which are not of formula (IA) may be made by analogous processes to those described above for compounds of formula (IA).

The starting materials for the above processes may be made by the methods set out in the Examples or by methods analogous thereto. Other conventional methods for making the starting materials will be evident to those skilled in the art.

The compounds of formula (I), and pharmaceutically acceptable salts thereof, are useful because they demonstrate pharmacological activity. In particular they demonstrate activity as kinase inhibitors, especially PKC inhibitors, e.g. as is shown by their activity in the in vitro assays described in Granet, R.A. et al, Analyt. Biochem. 1987; 163, 458-463; Olsson, H. et al, Cell Signal 1989, 1, 405-410; Chakravarthy, B.R. et al, Analyt. Biochem. 1991, 196, 144-150 and Bergstrand, H et al, J. Pharm. Exp. Ther. 1992; 263(3), 1334-1346.

In appropriate cellular systems, the compounds of formula (I) and pharmaceutical acceptable salts thereof, can also reduce the generation of inflammatory mediators. For example, the compounds can inhibit oxygen radical generation and generation of pro-inflammatory cytokines in monocytes. The compounds are especially useful as inhibitors of one or more cytokines selected from IL-1β, TNF-α, GM-CSF or IL-8.

The compounds of the invention are indicated for use in the treatment of inflammatory, immunological, bronchopulmonary, cardiovascular, oncological or CNS-degenerative disorders. Preferably for oral or topical treatment of inflammatory and/or immunological disorders, such as the oral or topical treatment of airway diseases involving inflammatory conditions, e.g. asthma, bronchitis or atopic diseases, e.g. rhinitis or atopic dermatitis; inflammatory bowel diseases, e.g. Crohn's disease or colitis; autoimmune diseases e.g. multiple sclerosis, diabetes, atherosclerosis, psoriasis, systemic lupus erythematosus or rheumatoid arthritis; malignant diseases, e.g. skin or lung cancer; HIV infections or AIDS; or for inhibiting rejection of organs/transplants.

The dose of the compound to be administered will depend upon the relevant indication, the age, weight and sex of the patient and may be determined by a physician. The dosage will preferably be in the range of from 0.1mg/kg to 100mg/kg.

The compounds may be administered topically, e.g. to the lung and/or the airways, in the form of solutions, suspensions, HFA aeosols or dry powder formulations, e.g. formulations in the inhaler denice known as the Turbuhaler® ; or systemically, e.g. by oral administration in the form of tablets, pills, capsules, syrups, powders or granules, or by

parenteral administration, e.g. in the form of sterile parenteral solutions or suspensions, or by rectal administration, e.g. in the form of suppositories.

The compounds of the invention may be administered on their own or as a pharmaceutical composition comprising the compound of the invention in combination with a pharmaceutically acceptable diluent, adjuvant or carrier. Particularly preferred are compositions not containing material capable of causing an adverse, e.g. an allergic, reaction.

Dry powder formulations and pressurized HFA aerosols of the compounds of the invention may be administred by oral or nasal inhalation. For inhalation the compound is desireably finely divided. The finely divided compound preferably has a mass median diameter of less than 10 μm, and may be suspended in a propellant mixture with the assistance of a dispersant, such as a C_8-C_{20} fatty acid or salt thereof, (e.g. oleic acid), a bile salt, a phospholipid, an alkyl saccharide, a perfluorinated or polyethoxylated surfactant, or other pharmaceutically acceptable dispersant.

The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

One possibility is to mix the finely divided compound with a carrier substance, e.g. a mono-, di- or polysaccharide, a sugar alcohol, or an other polyol. Suitable carriers are sugars, e.g. lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol; and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug

reservoir of a multidose inhaler, e.g. that known as the Turbuhaler® in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active compound, with or without a carrier substance, is delivered to the patient.

For oral administration the active compound may be admixed with an adjuvant or a carrier, e.g. lactose, saccharose, sorbitol, mannitol; a starch, e.g. potato starch, corn starch or amylopectin; a cellulose derivative; a binder, e.g. gelatine or polyvinylpyrrolidone, and/or a lubricant, e.g. magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

For the preparation of soft gelatine capsules, the compound may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above mentioned excipients for tablets. Also liquid or semisolid formulations of the drug may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing the compound, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

The compounds of the invention may also be administered in conjunction with other compounds used for the treatment of the above conditions.

The term 'medical therapy' as used herein is intended to include prophylactic, diagnostic and therapeutic regimens carried out in vivo or ex vivo on humans or other mammals.

Compounds of the present invention include all stereoisomers, pure and mixed racemates, and mixtures thereof.

In compounds of formula (IA) of the present invention, the following independent preferences apply:

-R_5 and/or R_6 carries a hydroxy or amino group,

-at least one of **Y** and **Z** are substituted ,

-position 5 of the indole is substituted,

-at least one of **Y** and **Z** are substituted with halo, methoxy or carboxylic ester,

-R_9 is H or alkyl and is most preferably H,

-when R_5 or R_6 is an aminodeoxysugar, it is preferably a six membered ring,

-when R_5 and R_9 together form a cyclic moiety, it is preferably a six membered ring,

-three or four of **X,Y,Z** and **A** are carbon, and/or

-R_1 and R_2, R_2 and R_3,or R_3 and R_4; and most preferably R_2 and R_3, form an annulated aromatic ring .

The most preferred compounds of the present invention are as follows:

3-[3-(4-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate,

3-[3-(6,7-Dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate,

3-[3-(6,7-Dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-5-methoxycarbonyl-indol-1-yl]-propyl-ammonium acetate,

3-[3-(6,7-Dichloro-4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-5-methoxycarbonyl-indol-1-yl]-propyl-ammonium acetate,

3-[5-Methoxycarbonyl-3-(7-methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate,

3-[3-(4-tert-Butoxycarbonylmethyl-7-methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-5-methoxycarbonyl-indol-1-yl]-propyl-ammonium acetate,

3-[3-(4-(3-Ammoniumpropyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium bis trifluoroacetate,

Dimethyl-{3-[3-(1-methyl-1H-indol-3-yl)-2-oxo-2H-quinoxalin-1-yl]-propyl}-ammonium trifluoroacetate,

3-[3-(3-Oxo-3,4-dihydro-benzo[g]quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate,

3-[6-Benzyloxy-3-(7-methoxy-4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate,

3-[5-Benzyloxy-3-(4-tert-butoxycarbonylmethyl-7-methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate,

3-[2-(4-Chloro-phenyl)-3-(7-methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate,

3-[2-(4-Chloro-phenyl)-3-(7-methoxy-4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate,

3-[3-(6,7-Dichloro-4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-2-ethyl-indol-1-yl]-propyl-ammonium acetate,

3-[3-(5-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-6-nitro-indol-1-yl]-propyl-ammonium acetate,

3-[6-Nitro-3-(6-nitro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate,

4-[3-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-ylmethyl]-benzyl-ammonium acetate,

3-[3-(4-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-ylmethyl]-benzyl-ammonium trifluoroacetate,

3-[3-(4-Benzyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium trifluoroacetate;

and the corresponding free amines thereof and other pharmaceutically acceptable salts thereof.

The most preferred compound of the present invention is:

3-[3-(3-Oxo-3,4-dihydro-benzo[g]quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate,

and the corresponding free amines thereof and other pharmaceutically acceptable salts thereof.

The following Examples illustrate, but in no way limit the invention.

All reactions were performed in dried glassware under Ar or N_2 unless otherwise noted. Tetrahydrofuran was distilled from sodium/benzophenone. Dimethyl formamide was distilled from calcium hydride, or dried over molecular sieves. Other solvents and all commercial reagents were used as received.

^1H - NMR spectra were recorded on a Varian XL-300 or Unity-500+ instrument. The central solvent peaks of chloroform-*d* (δ_H 7.24 ppm), methanol-d_4 (δ_H 3.34 ppm) and dimethyl sulphoxide-d_6 (δ_H 2.50 ppm) were used as internal references. Low-resolution mass spectra and accurate mass determinations were recorded on an Autospec-Q, Fisons Analytical, double focusing sector instrument equiped with a LSIMS interface.

Example 1

{1-[3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-propyl]-1H-indol-3-yl}-oxoacetic acid 2,5-dioxopyrrolidin-1-yl ester) [intermediate]

1-[3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-propyl]-1H-indol (1.00 g, 3.29 mmol) was dissolved in dichloromethane (10 ml) and cooled to 0°C. Oxalylchloride (0.28 ml, 3.29 mmol) was added and the reaction kept at 0°C for 30 minutes before the addition of N-hydroxysuccinimide (0.38 g, 3.29 mmol) followed by careful addition of pyridine (0.53 ml, 6.57 mmol).

After stirring the reaction for 1 hour at room temperature brine (5%, 10 ml) was added and the phases separated, the organic phase was washed with brine (5%, 2 x 10 ml), dried over Na_2SO_4 followed by removal of the solvent *in vacuo*. Crystallisation of the crude product from ethyl acetate - hexane yields the title product, 1.06 g (69%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.36 (2H, p, *J* 6.9 Hz), 2.93 (4H, s), 3.82 (2H, t, *J* 6.5 Hz), 4.29 (2H, t, *J* 7.5 Hz), 7.33-7.44 (3H, m), 7.70-7.75 (2H, m), 7.78-7.83 (2H, m), 8.32-8.36 (1H, m), 8.50 (1H, s).

FAB-MS: m/z 474 [MH+]

Example 2

A) 3-[3-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

1,2-Phenylenediamine (0.021 g, 0.20 mmol) and the product of Example 1 (0.075 g, 0.16 mmol) was dissolved in tetrahydrofuran (1 ml). Stirring overnight yields 2-(3-(3-(3-oxo-3,4-dihydroquinoxalin-2-yl)-inol-1-yl)-propyl)-isoindol-1,3-dione as a yellow precipitate that was filtered off and washed with tetrahydrofuran.

^{1}H-NMR (500, MHz, DMSO-d6): δ 2.18 (2H, p, *J* 7.1 Hz), 3.71 (2H, t, *J* 6.6 Hz), 4.44 (2H, t, *J* 7.4 Hz), 7.26-7.36 (4H, m), 7.45 (1H, t, *J* 7.4 Hz), 7.67 (1H, d, *J* 8.3 Hz), 7.81-7.85 (2H, m), 7.85-7.89 (3H, m), 8,91 (1H, d, *J* 7.5 Hz), 9.03 (1H, s), 12.44 (1H, s, NH).

FAB-MS: m/z 449.3 [MH+]

The precipitate was suspended in tetrahydrofuran (1 ml) and aqueous methylamine (40%, 0.7 ml) was added. After stirring for 5 hours the solvent was removed *in vacuo*. 3-(1-(3-Aminopropyl)-1H-indol-3-yl)-1H-quinoxalin-2-one was crystallised from water and treated with aqueous acetic acid (1 M, 1 ml) to obtain the title compound as a yellow solid, 0.045 g (75%), after freeze drying.

^{1}H-NMR (500 MHz, CD_3OD): δ 1.92 (3H, s), 2.26 (2H, dt, *J* 15.7, 7.0 Hz), 2.92-2.98 (2H, m), 4.43 (2H, t, *J* 6.9 Hz), 7.28-7.40 (4H, m), 7.46 (1H, t, *J* 7.5 Hz), 7.56 (1H, d, *J* 7.5 Hz), 7.92 (1H, d, *J* 8.0 Hz), 8.87 (1H, s), 8.96 (1H, d, *J* 7.6 Hz).

FAB-MS: m/z 319.1 [MH+]

B) 3-[3-(6-Fluoro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

The title compound was prepared in 89% yield as described in A) starting from 4-fluoro-1,2-phenylenediamine.

^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.83 (3H, s), 1.99 (2H, p, *J* 7.1 Hz), 2.67 (2H, t, *J* 7.0 Hz), 4.42 (2H, t, *J* 7.0 Hz), 7.27-7.37 (4H, m), 7.67 (1H, d, *J* 7.6 Hz), 7.70 (1H, d, *J* 9.5 Hz), 8.91 (1H, d, *J* 7.9 Hz), 9.04 (1H, s).

FAB-MS: m/z 337.1 [MH+]

C) 3-[3-(7-Methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

The title compound was prepared in 83% yield as described in A) starting from 4-methoxy-1,2-phenylenediamine.

^{1}H-NMR (500 MHz, CD_3OD): δ 1.95 (3H, s), 2.29 (2H, dt, *J* 15.2, 6.8 Hz), 2.96-3.00 (2H, m), 3.96 (3H, s), 4.45 (2H, t, *J* 6.8 Hz), 7.13 (1H, dd, *J* 8.9, 2.6 Hz), 7.27 (1H, d, *J* 9.2 Hz), 7.32-7.39 (2H, m), 7.44 (1H, d, *J* 2.6 Hz), 7.59 (1H, d, *J* 7.9 Hz), 8.89 (1H, s), 8.99 (1H, d, *J* 7.5 Hz).

FAB-MS: m/z 349.1 [MH+]

D) 3-[3-(2-Oxo-1,2-dihydro-pyrido[2,3-b]pyrazin-3-yl)-indol-1-yl]-propyl-ammonium acetate

The title compound was prepared in 85% yield as described in A) starting from 2,3-diaminopyridine.

^{1}H-NMR (500 MHz, CD_3OD): δ 1.95 (3H, s), 2.30 (2H, dt, *J* 15.6, 7.1 Hz), 2.98-3.03 (2H, m), 4.47 (2H, t, *J* 7.0 Hz), 7.36-7.41 (2H, m), 7.58-7.62 (1H, m), 8.72 (1H, s), 8.96 (1H, s), 9.06-9.10 (1H, m), 9.18 (1H, s).

FAB-MS: m/z 320.1 [MH+]

E) 3-[3-(4-Hydroxy-6-oxo-5,6-dihydro-pteridin-7-yl)-indol-1-yl]-propyl-ammonium acetate

The title compound was prepared in 38% yield as described in A) starting from 5,6-diamino-4-hydroxypyrimidine.

^{1}H-NMR (500 MHz, DMSO-d_6/D_2O): δ 1.89 (3H, s), 2.08 (2H, p, *J* 7.0 Hz), 2.80 (2H, t, *J* 7.1 Hz), 4.45 (2H, t, *J* 7.1 Hz), 7.26-7.33 (2H, m), 7.66 (1H, d, *J* 8.1 Hz), 8.00 (1H, s), 8.91 (1H, d, *J* 7.5 Hz), 9.20 (1H, s).

FAB-MS: m/z 337.0 [M+]

F) 3-[3-(6-Oxo-5,6-dihydro-pteridin-7-yl)-indol-1-yl]-propyl-ammonium acetate

The title compound was prepared in 38% yield as described in A) starting from 5,6-diaminopyrimidine.

FAB-MS: m/z 320.2 [M+]

G) 3-[3-(5-Hydroxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

The title compound was prepared in 22% yield as described in A) starting from 2,3-diaminophenol.

FAB-MS: m/z 335.1 [MH+]

H) 3-[3-(3-Oxo-3,4-dihydro-pyrido[3,4-b]pyrazin-2-yl)-indol-1-yl]-propyl-ammonium acetate

The title compound was prepared in 38% yield as described in A) starting from 3,4-diaminopyridine.

FAB-MS: m/z 320.2 [MH+]

I) 3-[3-(8-Nitro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

The title compound was prepared in 79% yield as described in A) starting from 3-nitro-1,2-phenylenediamine.

FAB-MS: m/z 364.1 [MH+]

J) 3-[3-(6-Nitro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

The title compound was prepared in 55% yield as described in A) starting from 4-nitro-1,2-phenylenediamine.

FAB-MS: m/z 364.1 [MH+]

K) 3-[3-(6,7-Dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

The title compound was prepared in 93% yield as described in A) starting from 4,5-dichloro-1,2-phenylenediamine.

FAB-MS: m/z 387.0 [MH+]

L) 3-[3-(7-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

The title compound was prepared in 93% yield as described in A) starting from 4-methyl-1,2-phenylenediamine.

FAB-MS: m/z 333.2 [MH+]

M) 3-[3-(5-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

The title compound was prepared in 87% yield as described in A) starting from 3-methyl-1,2-phenylenediamine.

FAB-MS: m/z 333.2 [MH+]

N) 3-[3-(6,7-Dimethyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

The title compound was prepared in 89% yield as described in A) starting from 4,5-dimethyl-1,2-phenylenediamine.

FAB-MS: m/z 347.2 [MH+]

O) 3-[3-(6-Methoxycarbonyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

The title compound was prepared in 43% yield as described in A) starting from methyl 3,4-diaminobensoate.

FAB-MS: m/z 377.1 [MH+]

P) 3-[3-(6-Ethoxycarbonyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

The title compound was prepared in 78% yield as described in A) starting from ethyl 3,4-diaminobensoate.

FAB-MS: m/z 391.0 [MH+]

Q) 3-[3-(3-Oxo-6-trifluoromethyl-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

The title compound was prepared in 85% yield as described in A) starting from 4-trifluoromethyl-1,2-phenylenediamine.

FAB-MS: m/z 387.1 [MH+]

Example 3

3-[3-(4-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

A dispersion of sodium hydride, 55-60% in oil, (0.0075 g, 0.17 mmol) in dry dimethyl formamide (2 ml) was cooled to -20° C. A solution 2-{3-[3-(3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl}-isoindol-1,3-dione (0.050g, 0.11 mmol) in dry dimethyl formamide (2 ml), was added dropwise and the resulting mixture kept at -20° C for 5 min and then at room temperature for another 15 min. The reaction mixture was cooled to -20° C and methyl iodide (0.017g, 0.12 mmol, 7.7 µl) was added via a syringe. The resulting

solution was allowed to reach room temperature whereupon 12 ml of diethyl ether was added. After 2 h at room temperature, 2-{3-[3-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl}-isoindole-1,3-dione was precipitated.

The precipitate was collected by centrifugation, and then suspended in tetrahydrofuran (2 ml). Aqueous methylamine (1 ml) was added giving a homogenous light yellow solution. After stirring for 5 h, the free amine was precipitated. The solvent was evaporated and the precipitate suspended in 4 ml of water and then collected by centrifugation. The precipitate was treated with aqueous acetic acid (1 M, 1 ml) and freeze dried to give 0.019g (43%) of the title compound as a yellow solid.

^{1}H-NMR (400 MHz, CD_3OD): δ 1.95 (3H, s), 2.28 (2H, quintet, J 7.0 Hz), 2.97 (2H, bs), 3.85 (3H, s), 4.46 (2H, t, J 7.0 Hz), 7.30-7.40 (2H, m), 7.46 (1H, ddd, J 8.0, 7.2, 2.4 Hz), 7.56-7.62 (3H, m), 7.98 (1H, d, J 7.7Hz), 8.90 (1H, s), 8.99 (1H, d, J 7.3 Hz).

FAB-MS: m/z 333.0 [MH+]

Example 4

3-{1-(6-Amino-2,4,6-trideoxy-β-D-threo-hexopyranosyl)-1H-indol-3-yl}-1H-quinoxazolin-2-one trifluoro acetic acid salt

a) 3-{1-(3-O-Benzoyl-6-phthalimido-2,4,6-trideoxy-β-D-threo-hexopyranosyl)-1H-indol-3-yl}-1H-quinoxalin-2-one

1-(3-O-Benzoyl-6-phthalimido-2,4,6-trideoxy-β-D-threo-hexopyranosyl)-1H-indole (0.30 g, 0.62 mmol) was dissolved in dichloromethane (3 ml) and cooled to 0 °C. Oxalylchloride (65 µl, 0.74 mmol) was added and the reaction mixture kept at 0 °C for 15 min and then stirred at room temperature for another 45 minutes. N-hydroxysuccinimid (0.08 g 0.70 mmol) was added followed by careful addition of pyridine (0.10 ml, 1.23 mmol). The reaction mixture was stirred at room temperature for 16 hours and then washed twice with water. The organic layer was evaporated and the crude mixed with tetrahydrofuran (10 ml) and 1,2-diphenylenediamine (0.09g, 0.80 mmol) and stirred at room temperature for 16 hours. The resulting percipitate was collected by centrifugation, washed twice with ether and dried to give 0.12 g (32%) of the subtitle product.

^{1}H-NMR (400 Mhz, DMSO-d_6): δ 1.63-1.74 (1H, m), 2.31-2.40 (2H, m), 2.55-2.62 (1H, m), 3.76 (1H, dd, *J* 14.2, 5.4 Hz), 3.86 (1H, dd, *J* 14.0, 7.3 Hz), 4.29-4.38 (1H, m), 5.41-5.53 (1H, m), 6.08 (1H, dd, *J* 11.0, 1.9 Hz), 7.00 (1H, t, *J* 7.5 Hz), 7.22 (1H, t, *J* 7.5 Hz), 7.29-7.37 (2H, m), 7.45 (1H, d, *J* 7.5 Hz), 7.49 (1H, d, *J* 7.9 Hz), 7.52-7.59 (2H, m), 7.69 (1H, t, *J* 7.5 Hz), 7.85 (4H, bs), 7.88 (1H, d, *J* 8.1 Hz), 8.01-8.06 (2H, m), 8.86 (1H, d, *J* 8.1 Hz), 9.05 (1H, s), 12.49 (1H, s).

b) The product from step a) (52.0 mg, 0.08 mmol) was dispersed in 2 ml of tetrahydrofuran. Aqueous methylamine was added (1 ml) and the mixtrure stirred at room temperature for 17 hours. The reaction mixture was eveporated and the crude filtered through a short column of silica gel using CH_2Cl_2/MeOH/NH_3 (100/10/1) as eluent. The solvents were evaporated and the crude amine subjected to reverse-phase column chromatography using a pre-packed column (Merck Lobar, LiChroprep RP-8) and MeOH/H_2O/TFA (70/30/0.1) as the eluent. The fractions containing the product were partly evaporated and freeze dried to give 0.01g (24%) of the title product.

^{1}H-NMR (500 Mhz, DMSO-d_6): δ 1.27-1.37 (1H, m), 1.95-2.05 (2H, m), 2.29-2.37 (1H, m), 2.88-3.00 (1H, m), 3.04-3.13 (1H, m), 3.93-4.08 (2H, m), 5.23 (1H, bs), 5.91 (1H, dd, *J* 11.2, 1.8 Hz), 7.29-7.36 (4H, m), 7.46 (1H, t, *J* 7.4 Hz), 7.75 (1H, t, *J* 7.9 Hz), 7.79 (2H, bs), 7.89 (1H, d, *J* 8.0 Hz), 8.89-8.93 (1H, m), 9.09 (1H, s), 12.51 (1H, s).

FAB-MS: m/z 391 [MH+]

Example 5

3-[3-(4-(3-Ammoniumpropyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium bis trifluoroacetate

A mixture of sodium hydride, 55-60% in oil, (0.029 g, 0.67 mmol) and 2-{3-[3-(3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1yl]-propyl}-isoindol-1,3-dione (0.25g, 0.56 mmol) in dry dimethyl formamide (4 ml) was stirred at -20 °C for 10 min and then at room temperature for another 30 min. A solution of 2-(3-Bromopropyl)-isoindole-1,3-dione (0.20 g 0.75mmol) in 2 ml dimethyl formamide was added and the rection mixture stirred at room temperature for 30 min and then at 60 °C for 3 hours. The percipitate formed was separated by centrifugation, washed with ethyl acetate and dried. The crude percipitate was suspended in tetrahydrofuran (5 ml) and aqeuous methylamine (3ml) and stirred at room temperature for 3.5 hours. The solvent was evaporated and the residue washed with 10 ml of water. The crude mixture was subjected to reverse-phase column chromatography using a pre-packed column (Merck Lobar, LiChroprep RP-8) and MeOH/H_2O/TFA (70/30/0.1) as the eluent. The fractions containing the product were partly evaporated and freeze dried to give 0.02g (6%) of the title product.

^{1}H-NMR (500 Mhz, CD_3OD): δ 2.29 (2H, quintet, *J* 7.6 Hz), 2.39 (2H, quintet, *J* 7.1 Hz), 2.99 (2H, t, *J* 7.8 Hz), 3.20 (2H, t, *J* 7.3 Hz), 4.50 (2H, t, *J* 7.1 Hz), 4.84-4.89 (2H, triplett hidden under the solvent), 7.31 (1H, td, *J* 7.6 1.0 Hz), 7.36 (1H, td, *J* 7.8 1.2 Hz), 7.56-7.66 (3H, m), 7.78-7.84 (1H, m), 8.04-8.09 (1H, m), 8.36 (1H, s), 8.94 (1H, d, *J* 7.9 Hz).

FAB-MS: m/z 376 [MH+]

The following examples were prepared following the methods described above in Examples 1 to 4. Removal of protecting groups were performed according to standard literature methods.

Example 6

3-[3-(4-tert-Butoxycarbonylmethyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-2-methyl-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 447 [MH+]

Example 7

3-[5-Benzyloxy-3-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 439 [MH+]

Example 8

3-[3-(4-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-6-nitro-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 378 [MH+]

Example 9

3-[3-(4-tert-Butoxycarbonylmethyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-2-(4-chloro-phenyl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 544 [MH+]

Example 10

3-[2-Ethyl-3-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 361 [MH+]

Example 11

3-[6-Benzyloxy-3-(4-tert-butoxycarbonylmethyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 539 [MH+]

Example 12

3-[5-Methoxycarbonyl-3-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 391 [MH+]

Example 13

3-[3-(4,7-Dimethyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-2-methyl-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 361 [MH+]

Example 14

3-[5-Benzyloxy-3-(4-tert-butoxycarbonylmethyl-7-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 553 [MH+]

Example 15

3-[3-(4-tert-Butoxycarbonylmethyl-7-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-6-nitro-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 492 [MH+]

Example 16

3-[2-(4-Chloro-phenyl)-3-(4,7-dimethyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 457 [MH+]

Example 17

3-[3-(4-tert-Butoxycarbonylmethyl-7-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-2-ethyl-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 475 [MH+]

Example 18

3-[6-Benzyloxy-3-(4,7-dimethyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

453 [MH+]

Example 19

3-[3-(4-tert-Butoxycarbonylmethyl-7-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-5-methoxycarbonyl-indol-1-yl]-propyl-ammonium acetate

505 [MH+]

Example 20

3-[3-(4-tert-Butoxycarbonylmethyl-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-2-methyl-indol-1-yl]-propyl-ammonium acetate

516 [MH+]

Example 21

3-[5-Benzyloxy-3-(6,7-dichloro-4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

508 [MH+]

Example 22

3-[3-(6,7-Dichloro-4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-2-ethyl-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 430 [MH+]

Example 23

3-[3-(6,7-Dichloro-4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-5-methoxycarbonyl-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 460 [MH+]

Example 24

3-[5-Benzyloxy-3-(4-tert-butoxycarbonylmethyl-6-nitro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 584 [MH+]

Example 25

3-[3-(4-tert-Butoxycarbonylmethyl-6-nitro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-6-nitro-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 523 [MH+]

Example 26

3-[3-(4-tert-Butoxycarbonylmethyl-6-nitro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-5-methoxycarbonyl-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 536 [MH+]

Example 27

3-[5-Benzyloxy-3-(4,5-dimethyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 453 [MH+]

Example 28

3-[3-(4,5-Dimethyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-6-nitro-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 392 [MH+]

Example 29

3-[3-(4-tert-Butoxycarbonylmethyl-5-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-2-(4-chloro-phenyl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 558 [MH+]

Example 30

3-[5-Benzyloxy-3-(4-tert-butoxycarbonylmethyl-7-methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 569 [MH+]

Example 31

3-[3-(4-tert-Butoxycarbonylmethyl-7-methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-6-nitro-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 508 [MH+]

Example 32

3-[2-(4-Chloro-phenyl)-3-(7-methoxy-4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 473 [MH+]

Example 33

3-[3-(4-tert-Butoxycarbonylmethyl-7-methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-2-ethyl-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 491 [MH+]

Example 34

3-[6-Benzyloxy-3-(7-methoxy-4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 469 [MH+]

Example 35

3-[3-(4-tert-Butoxycarbonylmethyl-7-methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-5-methoxycarbonyl-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 521 [MH+]

Example 36

3-[6-Hydroxy-3-(7-methoxy-4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 379 [MH+]

Example 37

5-[3-(1H-Indol-3-yl)-6,7-dimethyl-2-oxo-2H-quinoxalin-1-yl]-pentyl-ammonium trifluoroacetate

FAB-MS: m/z 357 [MH+]

Example 38

3-(1-Butyl-5-methoxy-1H-indol-3-yl)-1H-quinoxalin-2-one

FAB-MS: m/z 348 [MH+]

Example 39

3-[5-Bromo-3-(3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-ylmethyl]-benzyl-ammonium acetate

FAB-MS: m/z 459 [MH+]

Example 40

Acetic acid 3-[3-(3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl ester

FAB-MS: m/z 362 [MH+]

Example 41

3-[3-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-2-phenyl-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 395 [MH+]

Example 42

10-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-6,7,8,9-tetrahydro-pyrido[1,2-a]indol-8-ylmethyl-ammonium acetate

FAB-MS: m/z 345 [MH+]

Example 43

1-Methyl-3-(1-methyl-1H-indol-3-yl)-1H-quinoxalin-2-one

FAB-MS: m/z 290 [MH+]

Example 44

N-{3-[3-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl}-acetamide

FAB-MS: m/z 361 [MH+]

Example 45

3-[3-(4-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 333 [MH+]

Example 46

3-[3-(4-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium trifluoroacetate

FAB-MS: m/z 333 [MH+]

Example 47

3-(1-Benzyl-1H-indol-3-yl)-1H-quinoxalin-2-one

FAB-MS: m/z 352 [MH+]

Example 48

4-[3-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-butyl-ammonium acetate

FAB-MS: m/z 333 [MH+]

Example 49

3-[3-(4-Benzyloxymethyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 439 [MH+]

Example 50

3-[3-(4-Ethyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium trifluoroacetate

FAB-MS: m/z 347 [MH+]

Example 51

3-[3-(7-Benzyl-4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 423 [MH+]

Example 52

3-[3-(4-Benzyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium trifluoroacetate

FAB-MS: m/z 409 [MH+]

Example 53

3-[3-(4-Butyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium trifluoroacetate

FAB-MS: m/z 375 [MH+]

Example 54

3-[3-(4-Allyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium trifluoroacetate

FAB-MS: m/z 359 [MH+]

Example 55

3-[3-(4-Methylcarbamoylmethyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium trifluoroacetate

FAB-MS: m/z 390 [MH+]

Example 56

3-[3-(4-tert-Butoxycarbonylmethyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium trifluoroacetate

FAB-MS: m/z 433 [MH+]

Example 57

3-[3-(4-Carboxymethyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium trifluoroacetate

FAB-MS: m/z 377 [MH+]

Example 58

3-(1-Methyl-1H-indol-3-yl)-1H-quinoxalin-2-one

FAB-MS: m/z 276 [MH+]

Example 59

3-[3-(7-Benzyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium trifluoroacetate

FAB-MS: m/z 409 [MH+]

Example 60

3-[3-(1-Methyl-1H-indol-3-yl)-2-oxo-2H-quinoxalin-1-yl]-propyl-ammonium trifluoroacetate

FAB-MS: m/z 333 [MH+]

Example 61

4-[3-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-ylmethyl]-benzyl-ammonium acetate

FAB-MS: m/z 381 [MH+]

Example 62

2-[3-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-ethyl-ammonium acetate

FAB-MS: m/z 305 [MH+]

Example 63

3-[3-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-ylmethyl]-benzyl-ammonium acetate

FAB-MS: m/z 381 [MH+]

Example 64

4-[3-(4-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-ylmethyl]-benzyl-ammonium trifluoroacetate

FAB-MS: m/z 395 [MH+]

Example 65

3-[3-(4-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-ylmethyl]-benzyl-ammonium trifluoroacetate

FAB-MS: m/z 395 [MH+]

Example 66

3-[2-Methyl-3-(3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 333 [MH+]

Example 67

3-[5-Benzyloxy-3-(3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 425 [MH+]

Example 68

3-[5-Amino-3-(3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 334 [MH+]

Example 69

3-[6-Nitro-3-(3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 364 [MH+]

Example 70

3-[2-(4-Chloro-phenyl)-3-(3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 429 [MH+]

Example 71

3-[2-Ethyl-3-(3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 347 [MH+]

Example 72

3-[6-Benzyloxy-3-(3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 425 [MH+]

Example 73

3-[5-Methoxycarbonyl-3-(3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 377 [MH+]

Example 74

3-[6-Hydroxy-3-(3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 335 [MH+]

Example 75

3-[2-Methyl-3-(7-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 347 [MH+]

Example 76

3-[5-Benzyloxy-3-(7-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 439 [MH+]

Example 77

3-[5-Amino-3-(7-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 348 [MH+]

Example 78

3-[3-(7-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-6-nitro-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 378 [MH+]

Example 79

3-[2-(4-Chloro-phenyl)-3-(7-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 444 [MH+]

Example 80

3-[2-Ethyl-3-(7-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 361 [MH+]

Example81

3-[6-Benzyloxy-3-(7-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 439 [MH+]

Example 82

3-[5-Methoxycarbonyl-3-(7-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 391 [MH+]

Example 83

3-[6-Hydroxy-3-(7-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 349 [MH+]

Example 84

3-[5-Benzyloxy-3-(6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 494 [MH+]

Example 85

3-[5-Amino-3-(6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 403 [MH+]

Example 86

3-[3-(6,7-Dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-6-nitro-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 433 [MH+]

Example 87

3-[2-(4-Chloro-phenyl)-3-(6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 498 [MH+]

Example 88

3-[3-(6,7-Dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-2-ethyl-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 416 [MH+]

Example 89

3-[6-Benzyloxy-3-(6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 494 [MH+]

Example 90

3-[3-(6,7-Dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-5-methoxycarbonyl-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 446 [MH+]

Example 91

3-[3-(6,7-Dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-6-hydroxy-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 404 [MH+]

Example 92

3-[2-Methyl-3-(6-nitro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 378 [MH+]

Example 93

3-[5-Benzyloxy-3-(6-nitro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 470 [MH+]

Example 94

3-[5-Amino-3-(6-amino-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 349 [MH+]

Example 95

3-[6-Nitro-3-(6-nitro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 409 [MH+]

Example 96

3-[2-Ethyl-3-(6-nitro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 392 [MH+]

Example 97

3-[6-Benzyloxy-3-(6-nitro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 470 [MH+]

Example 98

3-[5-Methoxycarbonyl-3-(6-nitro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 422 [MH+]

Example 99

3-[2-Methyl-3-(5-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 347 [MH+]

Example 100

3-[5-Benzyloxy-3-(5-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 439 [MH+]

Example 101

3-[5-Amino-3-(5-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 348 [MH+]

Example 102

3-[3-(5-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-6-nitro-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 378 [MH+]

Example 103

3-[2-(4-Chloro-phenyl)-3-(5-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 444 [MH+]

Example 104

3-[6-Benzyloxy-3-(5-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 439 [MH+]

Example 105

3-[5-Methoxycarbonyl-3-(5-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 391 [MH+]

Example 106

3-[5-Methoxycarbonyl-3-(5-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 349 [MH+]

Example 107

3-[3-(7-Methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-2-methyl-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 363 [MH+]

Example 108

3-[5-Benzyloxy-3-(7-methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 455 [MH+]

Example 109

3-[5-Amino-3-(7-methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 364 [MH+]

Example 110

3-[3-(7-Methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-6-nitro-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 394 [MH+]

Example 111

3-[2-(4-Chloro-phenyl)-3-(7-methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 460 [MH+]

Example 112

3-[2-Ethyl-3-(7-methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 377 [MH+]

Example 113

3-[6-Benzyloxy-3-(7-methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 455 [MH+]

Example 114

3-[5-Methoxycarbonyl-3-(7-methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 407 [MH+]

Example 115

3-[6-Hydroxy-3-(7-methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 365 [MH+]

Example 116

3-[1-(3-Hydroxy-propyl)-1H-indol-3-yl]-1H-quinoxalin-2-one

FAB-MS: m/z 320 [MH+]

Example 117

Dimethyl-{3-[3-(1-methyl-1H-indol-3-yl)-2-oxo-2H-quinoxalin-1-yl]-propyl}-ammonium trifluoroacetate

FAB-MS: m/z 361 [MH+]

Example 118

3-{3-[4-(2-Hydroxy-ethyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-propyl-ammonium acetate

FAB-MS: m/z 363 [MH+]

Example 119

3-[2-Benzyl-1-(3-hydroxy-propyl)-1H-indol-3-yl]-1H-quinoxalin-2-one

FAB-MS: m/z 410 [MH+]

Example 120

3-[2-Benzyl-3-(3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/z 409 [MH+]

Example 121

3-[1-(3-Ammonium-propyl)-1H-indol-3-yl]-1,5-dimethyl-2-oxo-1,2-dihydro-pyrido[2,3-b]pyrazin-5-ium bistrifluoroacetate

FAB-MS: m/z 348 [MH+]

Example 122

[3-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-acetic acid tert-butyl ester

FAB-MS: m/z 376 [MH+]

Example 123

[3-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-acetic acid

FAB-MS: m/z 320 [MH+]

Example 124

3-[2-Benzyl-1-(3-hydroxy-propyl)-1H-indol-3-yl]-1H-quinoxalin-2-one

FAB-MS: m/s 410 [MH+]

Example 125

3-[2-Benzyl-3-(3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/s 409 [MH+]

Example 126

[3-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-acetic acid tert butyl ester

FAB-MS: m/s 376 [MH+]

Example 127

[3-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-acetic acid

FAB-MS: m/s 320 [MH+]

Example 128

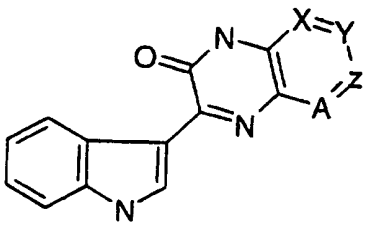
3-[3-(3-Oxo-3,4-dihydro-benzo[g]quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate

FAB-MS: m/s 369 [MH+]

The invention also provides the free bases of those of the above compounds which are exemplified as salts.

CLAIMS

1. An optionally substituted and/or annulated compound of formula (I):



(I)

wherein **X**, **Y**, **Z** and **A** is each independently carbon or nitrogen, and at least two of **X**, **Y**, **Z** and **A** are carbon;

and pharmaceutically acceptable salts thereof,

with the proviso that:

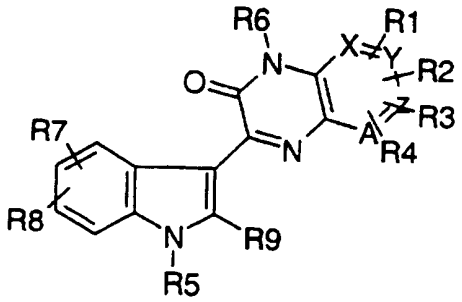
3-(1H-Indol-3-yl)-1H-quinoxalin-2-one,

3-(2-Methyl-1H-indol-3-yl)-1H-quinoxalin-2-one, and

3-(1,2-Diphenyl-1H-indol-3-yl)-1H-quinoxalin-2-one

are excluded from compounds of formula (I).

2. A compound according to claim 1, of formula (IA):



(IA)

wherein **X**, **Y**, **Z** and **A** are as defined in claim 1,

R_1, R_2, R_3, and R_4 is each independently H, hydroxy, amino, nitro, halo, C_{1-6} alkyl, phenylC_{1-6} alkyl, C_{1-6} alkoxy, haloC_{1-6} alkyl, carboxyC_{1-6} alkyl ester or R_1 and R_2 or R_2 and R_3 or R_3 and R_4 form an annulated aromatic ring, or when the atom to which it would be attached is nitrogen, is absent;

R_5 and R_6 is each independently H, C_{1-6} alkyl, hydroxyC_{1-6} alkyl, aminoC_{1-6} alkyl, phenylC_{1-6} alkyl, carboxyC_{1-6} alkyl, C_{1-6} alkenyl, (phenylC_{1-3} alkoxy)C_{1-3} alkyl, (C_{1-6} acyloxy)C_{1-6} alkyl, (C_{1-6} alkoxycarbonyl)C_{1-6} alkyl, (mono- or di-C_{1-6} alkyl)aminoC_{1-6} alkyl , (C_{1-6} alkyl)aminocarbonylC_{1-6} alkyl, (C_{1-6} acylamino)C_{1-6} alkyl, (aminoC_{1-3} alkylphenyl)C_{1-3} alkyl, or aminodeoxysugar;

R_7 and R_8 is each independently H, amino, nitro, hydroxy, halogen, C_{1-6} alkoxy, phenylC_{1-6} alkoxy or carboxyC_{1-6} alkyl ester;

R_9 is H, C_{1-6} alkyl, phenyl, halophenyl or phenylC_{1-6} alkyl and wherein when R_5 and R_9 together comprise3-5 carbons they may be linked to generate a cyclic moiety which may be aminoC_{1-6} alkyl substituted ;

and wherein at least one of R_1 to R_9 is not H and wherein when the only one of R_1 to R_9 which is not H is R_9, R_9 is not methyl;

and pharmaceutically acceptable salts thereof.

3. A compound according to claim 2, wherein at least one of R_5 and R_6 is aminoC_{1-6}alkyl.

4. A compound according to any of claims 1 to 3, wherein at least one of Y and Z is substituted.

5. A compound according to any one of claims 1 to 4, wherein at least one of **Y** and **Z** is substituted with halo, methoxy or carboxylic ester.

6. A compound according to any one of claims 1 to 5 wherein position 5 of the indole is substituted.

7. A compound according to any one of claims 2 to 6 wherein R_9 is H or alkyl.

8. A compound according to any one of claims 2 to 7 wherein R_5 or R_6 is an aminodeoxysugar, comprising a six membered ring.

9. A compound according to any one of claims 2 to 7 wherein R_5 and R_9 together form a six membered ring.

10. A compound according to any one of claims 1 to 9 wherein three or four of **X,Y,Z** and **A** are carbon.

11. A compound according to any one of claims 2 to10 wherein R_1 and R_2, or R_2 and R_3, or R_3 and R_4 form an annulated aromatic ring .

12. The compounds:

3-[3-(4-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate,

3-[3-(6,7-Dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate,

3-[3-(6,7-Dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-5-methoxycarbonyl-indol-1-yl]-propyl-ammonium acetate,

3-[3-(6,7-Dichloro-4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-5-methoxycarbonyl-indol-1-yl]-propyl-ammonium acetate,

3-[5-Methoxycarbonyl-3-(7-methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate,

3-[3-(4-tert-Butoxycarbonylmethyl-7-methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-5-methoxycarbonyl-indol-1-yl]-propyl-ammonium acetate,

3-[3-(4-(3-Ammoniumpropyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium bis trifluoroacetate,

Dimethyl-{3-[3-(1-methyl-1H-indol-3-yl)-2-oxo-2H-quinoxalin-1-yl]-propyl}-ammonium trifluoroacetate,

3-[3-(3-Oxo-3,4-dihydro-benzo[g]quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate,

3-[6-Benzyloxy-3-(7-methoxy-4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate,

3-[5-Benzyloxy-3-(4-tert-butoxycarbonylmethyl-7-methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate,

3-[2-(4-Chloro-phenyl)-3-(7-methoxy-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate,

3-[2-(4-Chloro-phenyl)-3-(7-methoxy-4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate,

3-[3-(6,7-Dichloro-4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-2-ethyl-indol-1-yl]-propyl-ammonium acetate,

3-[3-(5-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-6-nitro-indol-1-yl]-propyl-ammonium acetate,

3-[6-Nitro-3-(6-nitro-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate,

4-[3-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-ylmethyl]-benzyl-ammonium acetate,

3-[3-(4-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-ylmethyl]-benzyl-ammonium trifluoroacetate,

3-[3-(4-Benzyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium trifluoroacetate;

and other pharmaceutically acceptable salts thereof.

13. The compound:

3-[3-(3-Oxo-3,4-dihydro-benzo[g]quinoxalin-2-yl)-indol-1-yl]-propyl-ammonium acetate,

and other pharmaceutically acceptable salts thereof.

14. A free amine of a compound according to claim 12 .

15. A compound according to any one of claims 1 to 13, for use in medical therapy.

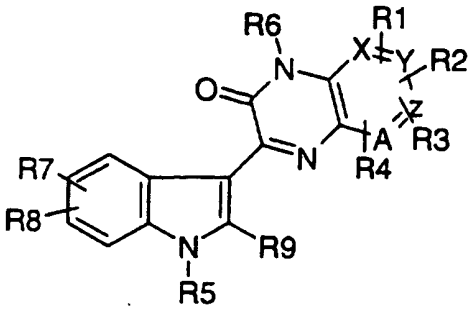
16. A compound according to claim 15 wherein the medical therapy is the treatment of inflammatory, immunological, bronchopulmonary, cardiovascular, oncological or CNS-degenerative disorders.

17. Use of a compound according to any one of claims 1 to 13 in the manufacture of a medicament for use in the treatment of inflammatory, immunological, bronchopulmonary, cardiovascular, oncological or CNS-degenerative disorders.

18. A method for the treatment of an inflammatory, immunological, bronchopulmonary, cardiovascular, oncological or CNS-degenerative disorder, wherein a therapeutically effective amount of a compound according to any one of claims 1 to 13 is administered to a mammal in the need of such treatment.

19. A pharmaceutical composition wherein the active ingredient is a compound according to any one of claims 1 to 13.

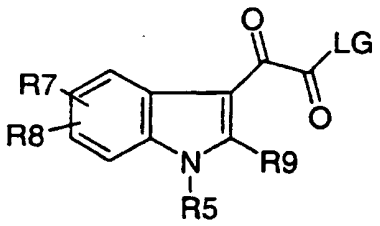
20. A compound of formula (II):



(II)

wherein **X, Y, Z, A,** are as defined in claim 1; R_1 to R_9 are as defined in claim 2 and at least one of R_5 and R_6 carries a protected amino, carboxy or hydroxy group, or

a compound of formula (III)



(III)

wherein R_5, R_7, R_8, and R_9 are as defined in claim 2, but when R_5 carries an amino, carboxy or hydroxy groups, such group is in a protected form; and LG is a leaving group.

21. A process for the preparation of a compound according to claim 2 when at least one of R_5 and R_6 of formula (IA) carries an amino, carboxy or hydroxy group, and pharmaceutically acceptable salts thereof, comprising:

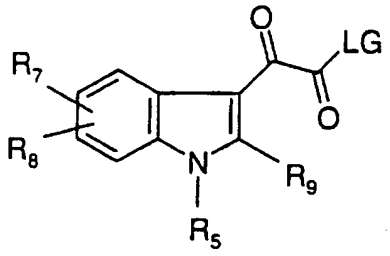
a) deprotecting a compound of formula (II) corresponding to formula (IA) but in which at least one of R_5 and R_6 carries protected amino, carboxy or hydroxy groups, or

b) converting a compound of formula (IA), in which at least one of R_5 and R_6 carries amino or carboxy groups

i) to a pharmaceutically acceptable salt thereof, or vice versa; or

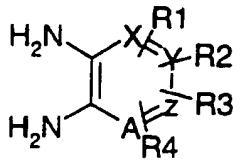
ii) a pharmaceutically acceptable salt of a compound of formula (IA) into a different pharmaceutically acceptable salt; or

when R_6 is hydrogen, comprising reacting a compound of formula (III):



(III)

wherein R_5, R_7, R_8, and R_9 are as defined in claim 2 and **LG** is a leaving group, with a compound of formula (IV):



(IV)

wherein R_1-R_4, are as defined in claim 2 and **A**, **X**, **Y**, and **Z** are as defined in claim 1;and when R_5 in formula (III) carries an amino, carboxy or hydroxy groups such groups are suitably protected and the protecting group removed in a subsequent deprotecting step; or

when R_6 is other than H, comprising reacting a compound of formula (II) which corresponds to formula (I), but in which R_6 is H, with a suitable alkylating agent in the

presence of a base and wherein when R_5 in formula (II) or the alkylating agent carries an amino, carboxy or hydroxy group, such group is suitably protected and the protecting group removed in a subsequent deprotecting step.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/01582

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 471/04, C07D 403/04, C07D 475/00, A61K 31/50
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts, Volume 82, No 13, 31 March 1975 (31.03.75), (Columbus, Ohio, USA), Glazunov, E. A. et al, "Riboflavine operon in Bacillus subtilis. VII. Biochemical investigation of mutants involved in early steps of biosynthesis", page 242, THE ABSTRACT No 82817b, Genetika 1974, 10 (11), 83-92	1-2,4,7
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A	EP 0072932 A2 (CASELLA AKATIENGESELLSCHAFT), 2 March 1983 (02.03.83)	1-17,19-21

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 February 1998	18 -02- 1998
Name and mailing address of the ISA/ Sw dish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/01582

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J. Med. Chem., Volume 39, 1996, Aviv Gazit et al, "Tyrphostins. 5. Potent Inhibitors of platelet-Derived Growth Factor Receptor Tyrosine Kinase: Structure-Activity Relationships in Quinoxalines, Quinolines, and Indole Tyrphostins" page 2170 - page 2177	1-17,19-21
X	EP 0328026 A1 (F. HOFFMANN-LA ROCHE & CO.), 16 August 1989 (16.08.89), example 1 and 8 (concerning intermediate III)	20
X	EP 0540956 A1 (F. HOFFMANN-LA ROCHE AG), 12 May 1993 (12.05.93), see example 1, 3-8 and 11-18 (concerning intermediate III)	20
X	EP 0490263 A1 (SYNTEX (U.S.A.) INC.), 17 June 1992 (17.06.92), see example 2 (concerning intermediate III)	20
X	FR 2182915 A (NELSON RESEARCH & DEVELOPMENT COMPANY), 14 December 1973 (14.12.73), see compound III and IV (concerning intermediate III)	20
X	US 4031221 A (GROVER C. HELSLEY ET AL), 21 June 1977 (21.06.77), see example 10, 12, 13 and 16 (concerning intermediate III)	20
X	EP 0464604 A2 (BRISTOL-MYERS SQUIBB COMPANY), 8 January 1992 (08.01.92), see example 13 (concerning intermediate III)	20
X	US 3642803 A (WILLIAM J. WELSTEAD ET AL), 15 February 1972 (15.02.72), see preparation 3 (concerning intermediate III)	20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/01582

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1500176 A (JOHN WYETH & BROTHER LIMITED), 8 February 1978 (08.02.78), concerning intermediate III) -- --------	20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/01582

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 18 and 19
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1

2. [X] Claims Nos.: 20
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Intermediate III include a great number of known compounds. This search report does therefore not include all relevant prior art.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see next sheet

1. [X] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

The subjects, defined by the problems and their means of solution, as listed below are so different from each other that no technical relationship or interaction can be appreciated to be present so as to form a single general inventive concept. The acceptance of a single general inventive concept covering the end products as well as products used to prepare these and products (intermediates) implies that when several claimed intermediates are implied in different reactions, these intermediates are technically closely inter-connected with the end products as well as with themselves by their use for incorporation of the same essential structural part into the end products.

This is not the case for the intermediate stipulated in claim 20 compound III.

Therefore, a single general inventive concept based on the relationship intermediates/end products is lacking and this leads to subjects as listed below, each falling under its own restricted inventive concept, defined by the nature of the essential structural part present in each intermediate and incorporated into the end product(s).

Invention 1. Claims 1-17, 19, 21 and claim 20 compound II

Invention 2. Claim 20 compound III

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/02/98

International application No.
PCT/SE 97/01582

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INTERNATIONAL SEARCH REPORT

Information on patent family members

03/02/98

International application No.
PCT/SE 97/01582

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